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EXAMINER

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DATE MAILED:

EXAMINER INTERVIEW SUMMARY RECORD

All participants (applicant, applicant's representative, PTO personnel):

(1) Ex. Ziska (3) ____

(2) Mr. Hallmer (4) ____

Date of interview 11/20/95 12:50 PM

Type: ☒ Telephonic ☐ Personal (copy is given to ☐ applicant ☐ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☐ No. If yes, brief description: NA

Agreement ~~☐ was reached with respect to some or all of the claims in question. ☐ was not reached.~~ NA

Claims discussed: NA

Identification of prior art discussed: NA

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: Applicant informed that the Office Action faxed on 11/17/95 has not been mailed and no response period set, as was agreed upon previously by Mr. Hallmer + Mr. Schwartz. The Office and the Examiner regret the confusion.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

☐ 1. It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph below has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW (e.g., items 1-7 on the reverse side of this form). If a response to the last Office action has already been filed, then applicant is given one month from this interview date to provide a statement of the substance of the interview.

☐ 2. Since the examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the substance of the interview unless box 1 above is also checked.

J/P [illegible signature]

This application has been returned to the examiner from the Board of Appeals and Interferences in view of the new art which has been submitted in the application for consideration by the examiner and in view of recently discovered applicable new art. The application is being returned to active status and the interference withdrawn in view of the new grounds of rejection, set forth below. Applicant's arguments, filed December 27, 1994, were considered in January, 1995 and resulted in the notification of initiation of interference proceedings by the examiner, communicated via telephone interview on January 25, 1995, paper no. 14, mailed January 31, 1995. Applicants' submission of new art in paper No. 16, filed February 24, 1995, in combination with the discovery of other pertinent patents have necessitated the new grounds of rejection based on art, set forth below.

Claims 83-103 are active and examined in this Office Action. Claims 1-67, 69-82 have been cancelled. Claim 68 remains active, but withdrawn from examination as being directed to non-elected subject matter. Claim 68 has never been cancelled.

The rejection of claims 16-18, 21-26, 75-81 under 35 U.S.C. 112, second paragraph, is withdrawn in view of the cancellation of the claims.

The rejection of claims 16-18, 21-26, 75-81 under 35 U.S.C. 112, first paragraph, regarding the limitation of the claims to mice, is withdrawn.

The rejection of claims 16-26 and 75-81 under 35 U.S.C. 103 as being unpatentable over Bruggemann taken with any of Joyner, Thomas, or Koller in further in view of Fell, is withdrawn in view of the cancellation of the claims.

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The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 83-103 are rejected under 35 U.S.C. § 103 as being unpatentable over Koller (U.S.P.N. 5,416,260) taken with Miller et al., Lorenz et al. and Bruggemann et al. Koller discloses a transgenic mouse having a lesion in its genome. Koller discloses the production of such mice wherein the lesion was created by using homologous recombination to create specific mutations in the embryonic stem cells and wherein the mutations were transferred to the germline (column 2). Koller discloses that the specific genes are inactivated or introduced in a site-directed

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fashion and that heterozygous hosts having one wild-type gene and one mutated gene could be mated to obtain homozygous hosts, so that all cells would have the appropriate modification (column 2). Koller discloses inactivation of at least one, preferably both, copies of a subunit of an MHC antigen, beta-2-microglobulin. Koller discloses that the method involves tranfections of cells with DNA associated with one of the loci related to beta-2-microglobulin. Koller discloses that the DNA will comprise at least a portion of the gene(s) at the particular locus with introduction of a lesion into at least one, usually both copies, of the native gene(s) so as prevent expression of a functional MHC antigen molecule. The lesion may be an insertion, deletion, replacement or combination thereof. Koller discloses alternatively homozygosity as to a phenotype may be achieved by breeding hosts heterozygous for the mutation. Koller discloses that the procedures for inactivating one or both copies of a particular MHC antigen will be similar, differing primarily in the choice of sequence, selectable marker used, and the method used to identify the absence of the MHC antigen. Since the procedures are analogous, the inactivation of the beta-2-microglobulin gene is used as an example and that substantially the same procedures, but with other genetic sequences, will suffice for the alpha and beta subunits of the Class II MHC antigens. Koller discloses in col. 5 that the homologous sequence for targeting the construct may have one or more deletions, insertions, substitutions or combinations thereof; preferably substitutions are employed and for an inserted gene of particular interest is a gene which provides a marker such as neomycin resistance. Koller discloses identifying the presence of a deletion when a deletion is introduced (column 5) and by identifying fragments which show the presence of the lesion(s) at the target gene site, one can identify cells in which homologous

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recombination has occurred to inactivate one of the two copies of the target gene (column 6). Koller discloses that the gene(s) which are introduced may also serve for protein production (column 7) where the proteins may be retained intracellular or be secreted. Koller discloses the transformation of ES cells for the purposes of making genetically transformed mice having a particular phenotype(column 8). Koller differs from the claims in that the reference fails to disclose a lesion of the J region in at least one copy of the immunoglobulin heavy chain locus. However, the secondary references, Miller, Bruggemann and Lorenz, cure the deficiency. Miller discloses that structural alterations in J regions of mouse immunoglobulin light chain lambda genes are associated with differential gene expression and that because each constant region of the lambda light chain gene is associated with only a single J region, the inactivation of a J lambda region would cause the entire gene to become nonfunctional and therefore would not result in the formation of a functional mRNA. Miller discloses that structural alterations can comprise deletions in the nucleotide sequence or alterations or insertions of other nucleotides. Miller further discloses that mouse kappa, the other type of light chain, and the heavy chain constant region genes are associated with four functional and one non-functional J gene segment. Lorenz discloses the structure of the human kappa locus and the nucleotide sequence of any particular region would have been readily available to one of skill in the art. Bruggemann discloses insertion of human immunoglobulin DNA into the germ line of mice wherein the human immunoglobulin DNA is in the germ-line configuration and contains human Vh, Dh, Jh and mu segments. Bruggemann discloses obtaining rearrangement of the human immunoglobulin heavy chain gene and the production of a human immunoglobulin heavy chain in transgenic mice. Bruggemann further discloses "This approach may allow the preparation of a

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repertoire of entirely human monoclonal antibodies that lack any sequence of rodent origin". Bruggemann discloses that the nucleotide sequence of large segments of the human heavy chain immunoglobulin locus was known and available to those of ordinary skill before the claimed invention was made.

It would have been obvious to one of ordinary skill to modify the mouse of Koller by inserting a lesion into the J region of the mouse heavy chain immunoglobulin gene in view of the teachings of Miller, that alterations of the J region sequence prevents the formation of an active mRNA, in order to produce a mouse having a modified genome with a lesion in the J region of the heavy chain gene. One of ordinary skill would have had a reasonable expectation of success in inserting a lesion into the heavy chain J region in view of the teachings of Koller that "substantially the same procedures, but with other genetic sequences" would suffice for use with other genes encoding other antigens (column 4, lines 58-63). One of ordinary skill would have been motivated to produce the mouse having a lesion in the J region in order to produce a mouse incapable of expressing endogenous mouse immunoglobulin heavy chains in view of the teachings of Bruggemann of the desirability of producing entirely human antibodies in mice (page 6709, columns 1 and 2, bridging paragraph) and page 6712, last paragraph, wherein Bruggemann states "It would be useful to have transgenic mice that have nonfunctional endogenous immunoglobulin gene loci so that they can make only human antibodies". Bruggemann therefore provides the motivation to combine the references since in order to have mice producing only human antibodies, one would need to prevent the expression of the endogenous mouse immunoglobulin genes and Miller discloses that expression can be prevented by inserting a lesion into the J region of an immunoglobulin chain.

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Regarding claim 84, Miller discloses lesions in the J region of the light chain gene disrupts expression and Koller discloses that insertions into one or both copies of a gene are possible by similar methods. Therefore, it would have been obvious to one of ordinary skill to insert lesions into both copies of the heavy chain gene, lacking evidence to the contrary, in order to obtain mice incapable of expressing endogenous immunoglobulins.

Regarding claim 85, it would have been obvious to one of ordinary skill to modify the mouse of Koller by inserting lesions into two copies of either the heavy chain locus, light chain locus or both, in view of the teachings of Bruggemann regarding the desirability of producing a repertoire of human monoclonal antibodies lacking any sequences of rodent origin. Note that the immunoglobulin "locus" is considered to comprise the V, D J and constant regions.

Regarding claims 86-88, Koller discloses that the modification of the genome at a particular locus can comprise an insertion and it would have been obvious to one of ordinary skill to insert the DNA encoding a human immunoglobulin heavy chain as disclosed by Bruggemann, or the DNA encoding a human immunoglobulin light chain locus, or both, in view of the teachings of Bruggemann of the desirability of producing a repertoire of entirely human antibodies lacking any sequences of rodent origin.

Regarding claims 89-94, Koller, Bruggemann and Miller disclose use of mice.

Regarding claims 95-103, Bruggemann discloses a human IgH minilocus and that the nucleotide sequence of large segments of the human immunoglobulin heavy chain locus were known and available to those of ordinary skill in the art. Lorenz discloses the structure of the human kappa locus and the nucleotide sequence of any particular region would have been readily

available to one of skill in the art. Both human immunoglobulin DNA sequences would be xenogeneic DNA sequences.

Accordingly, the modification of the mouse of Koller by inserting a lesion into the J region of an immunoglobulin heavy or light chain as suggested by Miller and by further insertion of a DNA encoding a xenogeneic immunoglobulin molecule as provided by Lorenz and Bruggemann in order to obtain a transgenic mouse comprising a modified genome comprising a lesion was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 83, 85, 86, 88, 89, 91, 92 and 94 are rejected under 35 U.S.C. § 103 as being unpatentable over Krimpenfort (U.S.P.N. 5,175,384). Krimpenfort discloses transgenic mice in which the T cell receptor gene in embryonic stem cells is inactivated using homologous recombination to insert into the genome a transgene encoding a lymphatic peptide variant which lacks a functional domain necessary for maturation of the lymphocytic cell type which would otherwise be provided by either or both of the suppressed endogenous alleles. In the cases where the lymphatic peptide variant is expressed, the variant is believed to be capable of suppressing expression of at least one set of cognate endogenous alleles normally expressed during differentiation of the precursor stem cell to the mature lymphocytic cell type. Krimpenfort discloses the analogous structure between the T cell receptor alpha chain and the immunoglobulin light chains. The T cell receptor is composed of two chains, the alpha and beta chains. The Ig light chain and the TCR alpha chain contains

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variable regions encoded by V and J segments only while the TCR beta chain and Ig heavy chain contain V regions encoded by V, D and J segments. The transgene encoding the TCRbeta variant chain lacks sequences encoding all or part of the variable region and the C region contained by such a lymphatic polypeptide variant is capable of suppressing the expression of endogenous TCR alleles thereby preventing the membrane expression of functional heterodimeric TCRs. Krimpenfort discloses that in the case of non-human transgenic animals substantially depleted in antibody secreting plasma cells (B cells as plasma cells), the transgene similarly encodes a lymphatic polypeptide variant containing at least the transmembrane sequence of the C region of the Ig heavy chain. Figure 2 of Krimpenfort discloses the genomic organization of the T cell receptor in mice and that the TCR beta chain is analogous to the Ig heavy chain in that the V region of each is composed of V, D and J segments and that the V region so formed is linked to the C region. Krimpenfort discloses that the lymphatic polypeptide corresponds to a naturally occurring polypeptide expressed selectively by lymphatic tissues and includes a wide variety of polypeptide chains associated with immunoglobulin production by plasma cells and TCRs produced by mature T cells; that such lymphatic polypeptides are produced by mature lymphocytic cells after differentiation and that such differentiation involves the functional rearrangement of numerous gene regions and segments to form the DNA sequence encoding the naturally occurring lymphatic polypeptide. Krimpenfort discloses that when transgenic mice are produced by the method the mice contain a functionally rearranged TCRbeta gene which has had approximately 90% of the V region deleted and that such mice failed to form a functional thymus and substantial T cell depletion was observed. Krimpenfort discloses that the transgene may encode a polypeptide wherein all or part of the variable

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region is deleted; but that the deleted sequences may also include part of the D and/or J segment of the variable region of the lymphatic polypeptide (column 8, lines 43-47). Krimpenfort discloses that transgenes may be derived from DNA sequences encoding one polypeptide chain of the Immunoglobulin molecule (column 9, lines 58-61) and that in the case of B cells, a derivative of the heavy chain of the Ig molecule is preferred to inhibit the formation of antibody producing plasma cells derived from B cells. Krimpenfort discloses that preferably the V region is deleted although 3' sequences encoding the C-terminal portion of the J segment may be retained and that transgenic mice containing immunoglobulin heavy chains wherein all or part of the variable region is deleted are expected to be incapable of producing plasma cells which secrete immunoglobulins and that because B cells rearrange the Ig heavy chains first and that once an Ig heavy chain is generated, light chain rearrangment begins. Krimpenfort discloses (column 10, lines (47-61) that the DNA sequence of the transgene may contain one or more mutations involving the insertion or deletion of one or more nucleotides that may, for example, result in a frame shift or nonsense mutation; and that the transgene has sufficient sequence homology with a cognate endogenous allele such that when introduced into an ES target cell it may homologously recombine with such an allele in the ES cell to disrupt its expression. Krimpenfort therefore suggests inserting a lesion into the genome using homologous recombination to inactivate endogenous genes by targeting a transgene containing a deletion to the D and/or J or constant region. Krimpenfort discloses that B and T cells probably use the same machinery for the assembly of Ig and TCR since B cells rearrange transfected TCR segments in the same way as transfected Ig gene segments (column 13) and Ig gene assembly in B cells closely parallels that for TCR assembly in T cells.

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Krimpenfort discloses that a preferred methodology is to clone a functionally rearranged heavy Ig gene and that the inserted rearranged gene would be expressed. Krimpenfort discloses mice having lesions in T cell receptor genes and differs from the claims in that the reference fails to disclose a mouse having a lesion in the J region of at least one copy of the immunoglobulin heavy chain locus. However, one of ordinary skill would have had a reasonable expectation of success in producing such a mouse in view of the teachings of Krimpenfort that the techniques for doing so were very similar to the techniques shown by him to result in a lesion in the T cell receptor gene. In view of the vast similarities in structure between the genes encoding the T cell receptor and the genes encoding the Ig heavy chain and in view of the specific teachings of Krimpenfort regarding the similarity of the procedures, one of ordinary skill would have had a reasonable expectation of success in producing a mouse having a lesion in the J region of the Ig heavy chain gene. One of ordinary skill would have been motivated to produce such a mouse in view of the teachings of Krimpenfort (column 4, lines 1-22) wherein Krimpenfort discloses that it is desirable to provide transgenic non-human animals substantially depleted in mature plasma cells, which are B cells.

Regarding claim 83, Krimpenfort discloses that an immunoglobulin transgene containing deletions in the V, D or J regions may be inserted into the genome using homologous recombination; that this transgene encodes the "lymphatic peptide variant"; and that the deletion in the inserted transgene results in the inability of the cognate endogenous alleles to be normally expressed since the transgene prevents rearrangement. Therefore, the inserted lesion results in the inability of the locus to rearrange or to produce a functional message since it is well known in the art and additionally taught by Krimpenfort that the

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immunoglobulin genes must rearrange in order to produce functional message encoding a heavy chain subunit. See column 8, lines 40-47, and column 7, lines 55-61.

Regarding claim 85, Krimpenfort clearly suggests inserting lesions into both copies of the genes in column 4, wherein it is disclosed "...the variant is believed to be capable of suppressing expression of at least one set of cognate endogenous alleles...".

Regarding claims 86 and 88, Krimpenfort discloses in column 7, lines 35-44, that "Thus, for examples, the alleles involved in TCRbeta chain production in mouse T cells are cognate endogenous alleles which may be suppressed by a transgene comprising a DNA sequence encoding a TCRbeta chain from mouse or other species" and therefore discloses insertion of a xenogeneic DNA sequence. It would have been obvious to one of ordinary skill to insert a DNA sequence encoding a xenogeneic heavy chain or light chain in view of the teachings of Krimpenfort that the transgene in addition to suppressing cognate endogenous alleles is also capable of facilitating the maturation of the particular lymphocytic cell type which would normally express the cognate endogenous alleles if the lymphatic polypeptide is expressed. B cells are known in the art to require partially rearranged heavy chain genes in order to complete differentiation to full antibody producing cells.

Accordingly, the modification of the mouse of Krimpenfort by substituting DNA encoding an Ig heavy chain lymphatic peptide variant having a lesion in the J region for the DNA encoding the TCRbeta chain lymphatic peptide variant was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success

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in producing the claimed invention and the invention as a whole is prima facie obvious.

Claims 84, 87, 90, 93 and 95-103 are rejected under 35 U.S.C. § 103 as being unpatentable over Krimpenfort as applied to claims 83, 85, 86, 88, 89, 91, 92 and 94 above, and further in view of Miller et al., Bruggemann et al. and Lorenz et al. Claims 83, 85, 86, 88, 89, 91, 92 and 94 were rejected for reasons as stated above. Miller discloses that structural alterations in J regions of mouse immunoglobulin light chain lambda genes are associated with differential gene expression and that because each constant region of the lambda light chain gene is associated with only a single J region, the inactivation of a J lambda region would cause the entire gene to become nonfunctional and therefore does not result in the formation of a functional mRNA. Miller discloses that structural alterations of the J region can comprise deletions in the nucleotide sequence or alterations or insertions of other nucleotides. Miller further discloses that mouse kappa, the other type of light chain, and the heavy chain constant region genes are associated with four functional and one non-functional J gene segment. Lorenz discloses the structure of the human kappa locus and the nucleotide sequence of any particular region would have been readily available to one of skill in the art. Bruggemann discloses insertion of human immunoglobulin DNA into the germ line of mice wherein the human immunoglobulin DNA is in the germ-line configuration and contains human Vh, Dh, Jh and mu segments. Bruggemann discloses obtaining rearrangement of the human immunoglobulin heavy chain gene and the production of a human immunoglobulin heavy chain in transgenic mice. Bruggemann further discloses "This approach may allow the preparation of a repertoire of entirely human monoclonal antibodies that lack any sequence of rodent origin". Bruggemann discloses that the nucleotide sequence of large

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segments of the human heavy chain immunoglobulin locus was known and available to those of ordinary skill before the claimed invention was made.

It would have been obvious to one of ordinary skill to modify the mouse of Krimpenfort by inserting a lesion into the J region of the mouse light chain immunoglobulin gene in view of the teachings of Miller, that alterations of the J region sequence prevents the formation of an active mRNA, in order to produce a mouse having a modified genome with a lesion in the J region of the heavy chain gene. In view of the vast similarities in structure between the genes encoding the T cell receptor and the genes encoding the Ig heavy chain and in view of the specific teachings of Krimpenfort regarding the similarity of the procedures, one of ordinary skill would have had a reasonable expectation of success in producing a mouse having a lesion in the J region of the Ig light chain gene.One of ordinary skill would have been motivated to produce the mouse having a lesion in the J region in order to produce a mouse incapable of expressing endogenous mouse immunoglobulin light chains in view of the teachings of Bruggemann of the desirability of producing entirely human antibodies in mice (page 6709, columns 1 and 2, bridging paragraph) and page 6712, last paragraph, wherein Bruggemann states "It would be useful to have transgenic mice that have nonfunctional endogenous immunoglobulin gene loci so that they can make only human antibodies". Bruggemann therefore provides the motivation to combine the references since in order to produce only human antibodies in mice, one would need to prevent the expression of the endogenous mouse immunoglobulin genes and Miller discloses that expression can be prevented by inserting a lesion into the J region of an immunoglobulin chain.

Regarding claim 84, Miller discloses lesions in the J region of the light chain genes disrupt expression and Krimpenfort

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discloses that insertions into one or both copies of a gene are possible by similar methods since both must be inactivated in order to completely disrupt endogenous expression and deplete T cells and B cells.

Regarding claim 87, Krimpenfort discloses in column 7, lines 35-44, that "Thus, for examples, the alleles involved in TCRbeta chain production in mouse T cells are cognate endogenous alleles which may be suppressed by a transgene comprising a DNA sequence encoding a TCRbeta chain from mouse of other species" and therefore discloses insertion of a xenogeneic DNA sequence. It would have been obvious to one of ordinary skill to insert a DNA sequence encoding a xenogeneic heavy chain or light chain in view of the teachings of Krimpenfort that the transgene is addition to suppressing cognate endogenous alleles is also capable of facilitating the maturation of the particular lymphocytic cell type which would normally express the cognate endogenous alleles if the lymphatic polypeptide is expressed. B cells are known in the art to require partially rearranged heavy chain genes in order to complete differentiation to full antibody producing cells.

Regarding claim 90, Krimpenfort, Bruggemann and Miller disclose use of mice.

Regarding claims 95-103, Bruggemann discloses a human IgH minilocus and that the nucleotide sequence of large segments of the human immunoglobulin heavy chain locus were known and available to those of ordinary skill in the art. Lorenz discloses the structure of the human kappa locus and the nucleotide sequence of any particular region would have been readily available to one of skill in the art. Both human immunoglobulin DNA sequences would be xenogeneic DNA sequences.

Accordingly, the modification of the mouse of Krimpenfort by substituting a lesion into the J region of an immunoglobulin

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light chain as suggested by Miller, Bruggemann and Lorenz in order to obtain a transgenic mouse comprising a modified genome comprising a lesion was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

No claim is allowed.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO FAX center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (30 November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Suzanne Ziska, Ph.D., whose telephone number is (703)308-1217. In the event the examiner is not available, the examiner's supervisor, Ms. Jacqueline Stone, may be contacted at phone number (703) 308-3153.

SUZANNE E. ZISKA
PRIMARY EXAMINER
GROUP 1800

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